

# CONNEXIN 26 GENE TESTING

## COULD MY HEARING LOSS BE CAUSED BY MUTATIONS IN THE CONNEXIN 26 GENE?

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Mutations in the connexin 26 (Cx26) gene are the most common cause of hearing loss. Cx26 hearing loss is most often seen in a person with:

- Hearing loss that was found at birth or in early childhood
- Hearing loss that is mild, moderate, severe or profound
- Hearing loss without any other medical problems (nonsyndromic)
- Hearing loss with no identified cause

Although these are the most common characteristics of hearing loss due to a mutation in Cx26, there can be variations, even within a family. There have been several occasions when skin disorders have been found in people with deafness due to dominant Cx26 mutations. Furthermore, there have been instances when a child's deafness was originally thought to be due to non-hereditary factors (*e.g.*, an infection or exposure to antibiotics) and then the child was later found to have mutations in Cx26. In such cases, it is more likely that the child's deafness was caused by the Cx26 mutations than by environmental agents. It should also be noted that many children with Cx26 mutations have no family history of hearing loss.

## WHY SHOULD I HAVE CX26 TESTING?

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Cx26 testing can help identify the cause of the hearing loss as well as help predict the prognosis of the hearing loss (most Cx26 hearing loss does not worsen). It can also help with treatment decisions (most Cx26 hearing loss responds well to hearing aids and/or cochlear implants). In addition, identifying Cx26 mutations as the cause of a person's hearing loss will reduce the need to perform other clinical tests. Furthermore, a positive test result can assure the family that no other problems associated with a syndromic form of hearing loss will develop. Testing can also help predict the likelihood that future children in the family will be born with hearing loss.

## HOW IS THE CX26 GENE TEST PERFORMED?

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To perform the Cx26 test, a DNA sample is obtained and your Cx26 gene sequence is compared to that of the regularly occurring sequence to look for changes. Some laboratories examine the entire sequence of the Cx26 gene, whereas other laboratories only search for common mutations, such as 35delG, the most common mutation in the Caucasian population. Some laboratories may combine these methods by first screening for a common mutation and then, in certain circumstances, sequencing the whole gene. It is recommended that your doctor choose a lab that will look at the whole coding sequence of the gene. If the lab does not sequence the whole gene, less common mutations could easily be missed.

## HOW ARE THE RESULTS OF A Cx26 TEST INTERPRETED?

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There are four possible outcomes of a Cx26 test:

1. *Two Cx26 mutations are found.* If two identical mutations (e.g., 35delG/35delG) or two different mutations (e.g., 35delG/167delT) are found, it can be assumed that the patient's hearing loss is caused by the Cx26 mutations.
2. *No Cx26 mutations are detected.* If no mutations are found, one must first consider how the test was performed. Was the whole coding sequence of the gene analyzed or was the gene only screened for the most common mutation(s)? If the whole coding sequence was analyzed and no mutations were found, it is unlikely that the patient's hearing loss was caused by Cx26 mutations.
3. *Only one Cx26 mutation is detected.* If only one mutation is detected, interpretation can be difficult. The most likely explanations are:
  - A) The Cx26 mutation may be unrelated to the deafness. Many people (approximately 3%) have, or "carry", single Cx26 mutations but are not hearing impaired. As such, it is possible for a person with hearing loss to carry a single Cx26 mutation but have hearing loss is due to another gene or a non-genetic cause. It should be noted that the correct name of this gene is GJB2 (gap junction beta 2). We use the protein name, connexin 26, because it is more common to the public.
  - B) The test did not detect the second mutation. Even though examining the whole coding sequence of the gene will detect most mutations, there are other regions of the gene sequence and surrounding DNA that could contain a mutation. Unfortunately, these sequences are rarely analyzed unless a specific mutation is already known.
  - C) The mutation may act as a dominant mutation, meaning that only one mutation is required to cause hearing loss. A list of the known dominant mutations for Cx26 can be found at <http://www.crg.es/deafness>
  - D) There may be a mutation in another gene for a protein called connexin 30 that may work together with the Cx26 mutation to cause hearing loss. (Have your doctor check to see if the lab can test for the Cx30 deletion.)
4. *Cx26 mutations are detected but their significance is unknown.* Some changes in the Cx26 gene are not considered to affect the function of the gene. These changes are often called "polymorphisms". Sometimes, a new mutation is found and it is not yet clear whether the change will cause hearing loss or not. Unfortunately, more studies would need to be done before a definite conclusion could be made.

A catalog of all Cx26 mutations can be found at the "Connexins and Deafness" website (<http://www.crg.es/deafness>). It should be noted that the correct name of this gene is GJB2 (gap junction beta 2). We use the protein name, connexin 26, because it is more common to the public.